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Review

Shared components of mitochondrial and peroxisomal division

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Abstract

Mitochondria and peroxisomes are ubiquitous subcellular organelles, which are highly dynamic and display large plasticity. Recent studies have led to the surprising finding that both organelles share components of their division machinery, namely the dynamin-related protein DLP1/Drp1 and hFis1, which recruits DLP1/Drp1 to the organelle membranes. This review addresses the current state of knowledge concerning the dynamics and fission of peroxisomes, especially in relation to mitochondrial morphology and division in mammalian cells.

Keywords: Dynamin; Fission; Fis1; Mitochondria; Peroxisome; Pex11

1. Peroxisomes in brief

Peroxisomes were first isolated from rat liver and biochemically characterized by De Duve and Baudhuin [1]. They discovered that peroxisomes contained several H_2O_2-producing oxidases as well as catalase, a H_2O_2-degrading enzyme. To emphasize these chemical properties, De Duve introduced the functional term "peroxisome", which gradually replaced the former morphological designation, "microbody", coined by Rhodin [2]. With the invention of the alkaline 3, 3′-diaminobenzidine (DAB) reaction for catalase, it became possible to specifically stain these organelles for light and electron microscopy [3,4]. This cytochemical procedure revealed that peroxisomes, like mitochondria, are ubiquitous subcellular organelles which are present in nearly all eukaryotic cells, including unicellular eukaryotes. Whereas mitochondria (0.5–0.7 μm in diameter) are double membrane-bound organelles containing their own genomes and transcription/translation systems, peroxisomes (0.1–1 μm in diameter) are morphologically characterized by a single limiting membrane and a fine granular matrix devoid of DNA. Another remarkable finding was the discovery of a fatty acid β-oxidation system in peroxisomes, which coexists (and cooperates) with the mitochondrial fatty acid β-oxidation system in mammalian cells [5–7]. This discovery was made by studies with several structurally dissimilar hypolipidemic drugs and plasticizers (so called "peroxisome proliferators") which remarkably increased the number and size of peroxisomes and the synthesis of peroxisomal enzymes, especially in the livers of rodents [8,9]. Evidence also suggests that the xenobiotic-induced proliferation of peroxisomes is accompanied by the formation of hepatic tumors [10–12]. The importance of peroxisomes in mammalian (and human) metabolism and disease became clear in the 1980s, when their major role in the β-oxidation of very-long-chain fatty acids (VLCFA) and in the biosynthesis of ether glycerolipids (plasmalogens) was discovered [13–15] in conjunction with Zellweger syndrome, a genetic neurodegenerative peroxisomal disorder [16,17]. Since then, the "Cinderella" among the subcellular organelles, which had long been regarded as the cell's dust bin, changed image and turned into a princess. At present, more than 50 enzymes have been described in mammalian peroxisomes, which are involved in diverse metabolic pathways (such as peroxide metabolism; α- and β-oxidation of certain fatty acids; metabolism of amino acids and glyoxylate; catabolism of purines, polyamines, prostaglandins and eicosanoids) including several anabolic reactions (e.g., the biosynthesis of ether lipids (plasmalogens), bile acids, cholesterol and dolichol, fatty acid elongation) [18,19]. It should be

Abbreviations: DLP, dynamin-like protein; Drp, dynamin-related protein; ER, endoplasmic reticulum; Fip, Fis1 interacting protein; Pex, peroxin; PMP, peroxisomal membrane protein; PTS, peroxisomal targeting signal

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noted that peroxisomes in plants, yeasts and protozoa generally possess a far wider spectrum of activities than in vertebrates. In trypanosomes, for example, the peroxisomes harbour glycolytic enzymes (therefore called glycosomes) [20]; in filamentous fungi, they are involved in the biosynthesis of penicillin [21]; in plants, they play an important role in the glyoxylate cycle (therefore called glyoxysomes) and in photorespiration [22,23], and in the firefly (*Photinus pyralis*) peroxisomes in cells of the lantern organ contain luciferase which catalyzes a light-producing bioluminescent reaction [24,25]. Recent studies have revealed the involvement of plant and mammalian peroxisomes in the metabolism of oxygen free radicals and nitric oxide that have important functions in cellular signalling. Like mitochondria, mammalian peroxisomes are supposed to play an important role in a variety of physiological and pathological processes involving reactive oxygen species (ROS) [26–28]. The enthusiasm for the investigation of peroxisomes has now focussed on the biogenesis of peroxisomes, the import of peroxisomal matrix and membrane proteins, and its relation to a number of inherited human disorders. It becomes obvious from these ongoing studies that peroxisomes possess unique features which have often been in disagreement with existing dogmas in cell biology. In contrast to mitochondria and ER, for example, peroxisomes can import completely folded and even oligomeric proteins via a yet unknown mechanism (reviewed in [29–31]). Furthermore, recent findings suggest that peroxisomes can be formed de novo from the ER or a subdomain of the ER [32].

2. The biogenesis of peroxisomes

The metabolic functions of peroxisomes and their protein composition can vary greatly depending upon organism, cell type, developmental stage, and environmental conditions. Peroxisomes in almost all organisms have the remarkable ability to proliferate and multiply, or be degraded in response to nutritional and extracellular environmental stimuli [33,34]. In rodents, for example, peroxisome biogenesis (and thus, peroxisome number, size and expression of peroxisomal enzymes) is highly induced when activators of the peroxisome proliferator activated receptor-α (PPAR-α), which belongs to the family of nuclear transcription factors, are applied [8,9].

In contrast to mitochondria, peroxisomes are devoid of DNA and their own protein translation machinery, and all of their proteins are encoded by nuclear genes. Most of the peroxisomal proteins are synthesized on free polyribosomes in the cytoplasm and are then post-translationally directed to the organelle [35]. Sorting of peroxisomal matrix proteins is mediated by cytosolic receptors (Pex5p for PTS1 and Pex7p for PTS2) that recognize two well-characterized classes of peroxisomal targeting signals (PTS1 and PTS2). The PTS1 comprises a C-terminal tripeptide (SKL), whereas the PTS2 is located near the N-terminus. The majority of the identified *peroxins*, the proteins required for peroxisome biogenesis (Pexp), are involved in matrix protein import and contribute to the formation of the docking and translocation machinery at the peroxisomal membrane. Contrary to mitochondrial protein import, it is assumed that the soluble receptors accompany their cargo inside the peroxisomes and recycle back to the cytosol (*extended shuttle model*). Furthermore, peroxisomal proteins pass through the intact peroxisomal membrane in a folded or even oligomeric state, presumably by the formation of a transient membrane pore (for reviews, see [29,31,36,37]).

Molecular details on the import of peroxisomal membrane proteins (PMPs) are just beginning to emerge [30,38]. Positively charged amino acids adjacent to at least one hydrophobic patch or transmembrane domain appear to be important components of mPTS [39,40]. Until now, the peroxins Pex3p, Pex19p and Pex16p are implicated in PMP import. Recent evidence suggests that Pex19p functions as a cycling receptor/chaperone for PMPs, which is recruited to the peroxisome by the membrane receptor Pex3p [30,41,42].

The classical model of peroxisome biogenesis, proposed by Lazarow and Fujiki [35], predicts that peroxisomes grow by uptake of newly synthesized matrix and membrane proteins from the cytosol and multiply by division. Like mitochondria, peroxisomes are often found in close contact to the ER [43,44]. This led to the assumption that specific ER domains mediate the transport of phospholipids to the growing organelles by an as yet unknown mechanism. However, recent findings indicate that there is a direct link between peroxisomes and the ER [45–48]. There is compelling evidence that some peroxisomal proteins are routed indirectly to peroxisomes through the ER (e.g., Pex3p) by a yet unknown mechanism [32,49,50]. Furthermore, data have been reported for different yeasts (e.g., *Y. lipolytica*, *P. pastoris*) and mammalian cells supporting either de novo synthesis or the formation of pre-peroxisomal vesicles from ER subdomains [32,45,51,52]. This links peroxisomes to the secretory pathway [53], and has led to modifications of the growth and division model [45,46,48,54]. As some of the above data are based on recovery experiments, where peroxins have been re-introduced in cells lacking pre-existing peroxisomes, the physiological significance of the mechanism of peroxisome recovery in comparison to the classical pathway of growth and division is controversially discussed, especially in mammalian cells. In some yeasts, which possess only a few peroxisomes, it may represent a rescue mechanism that becomes functional in case peroxisomes are lost (e.g., due to failure in inheritance).

3. Peroxisomal and mitochondrial morphology

3.1. Mitochondrial morphology and dynamics—balanced fusion and fission

Mitochondria and peroxisomes are both dynamic organelles which have been shown to frequently change size and shape and to move in a motor protein-dependent manner along cytoskeletal tracks throughout the cell [55,56] (articles by L. Pon and G. Hajnoczky, this issue). Mitochondria take various shapes, including small, bean-shaped or spherical structures, elongated tubules or a single, interconnected tubulo-reticular network [57] (article by M. Yaffe, this issue). It is assumed that balanced membrane fission and fusion events are required for the

establishment and maintenance of mitochondrial morphologies [58]. Although the physiological significance of mitochondrial dynamics is not fully understood, there is growing evidence that the maintenance of the correct mitochondrial morphology by fission and fusion is critical for cell function (reviewed in [59]). This notion is supported by recent findings that mutations in genes encoding fission/fusion proteins cause human diseases [60–63] (and articles by A. Santel and P. Belenguer, this issue).

3.2. Peroxisomal morphology and dynamics—tubules and 'beads on a string'

Similar to mitochondria, the peroxisomal compartment displays a remarkable plasticity and complexity. Several morphologically distinct types of peroxisomes have been described in mammalian tissues and cell lines, first by electron microscopic studies [64–67], and later at the light microscopic level [68–71]. Peroxisomes can appear as spherical organelles, but are also observed to form elongated, tubular structures and small, tubulo-reticular networks, which are frequently associated with lipid droplets [72] (Fig. 1). The tubulo-reticular peroxisomes are extremely dynamic, with constant formation of tubular extensions interconnecting or detaching [71,73]. A heterogeneous and more complex peroxisomal compartment is observed under conditions of rapid cellular growth, for example, after hepatectomy [66] or stimulation of cultured cells with defined growth factors, fatty acids or free radicals [74,75], suggesting the involvement of intracellular signalling in peroxisome elongation. The formation of tubular peroxisomes was also induced by microtubule depolymerization [76], or by overexpression of Pex11pβ, a prominent peroxisomal membrane protein, supposed to be involved in growth and division of peroxisomes [77] (see Section 5.1). Interestingly, tubular peroxisomes often showed a 'beads on a string'-like appearance before they were observed to fragment into spherical peroxisomes (Fig. 1). Based on these observations, it has become evident in the last years that tubulation and fission of elongated peroxisomes contributes to peroxisome proliferation and represents processes of peroxisomal growth and division (Figs. 1, 2). Furthermore, tubule formation of peroxisomes appears to be an important aspect of peroxisome division [73,76,77].

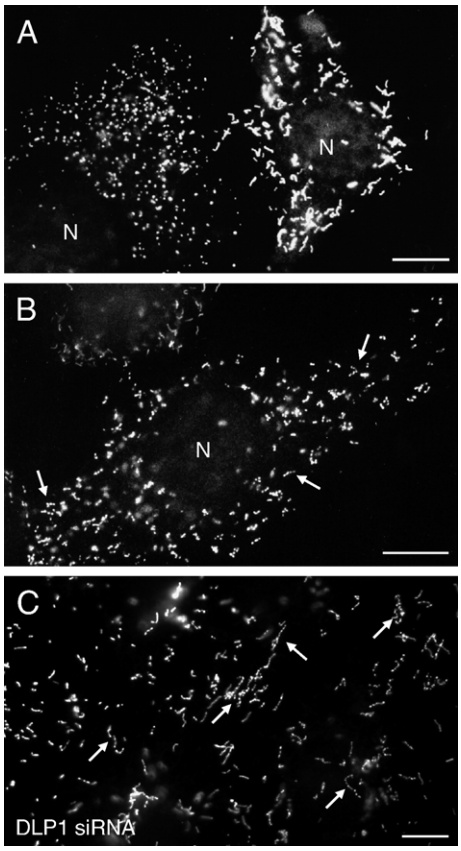

Fig. 1. Peroxisomal shape and distribution in cultured mammalian cells. Peroxisomes in HepG2 cells (A, B), a human hepatoblastoma cell line, and in COS-7 cells (C), a green monkey kidney cell line, were visualized by immunofluorescence using specific antibodies directed to the peroxisomal matrix protein catalase (A, B), or to PMP70, a peroxisomal membrane protein (C). (A) Mammalian cells can exhibit different peroxisomal shapes under normal culture conditions. Note the spherical shape of peroxisomes in the cell at the left, in contrast to their elongated, tubular morphology in the cell at right. Peroxisomes show a uniform intracellular distribution. In panel B peroxisomes appear like 'beads on a string' (arrows) indicating the formation of spherical peroxisomes by fission from tubular ones. (C) Silencing of DLP1/Drp1 by siRNA results in the formation of highly elongated and constricted peroxisomes (arrows). Division into spherical organelles is completely inhibited. N, nucleus. Scale bars, 10 μm.

4. Peroxisomal and mitochondrial division

4.1. Lessons from mitochondrial division—the players

Organelle fission and fusion events are important for the regulation of morphology and number, which plays an essential role in organelle inheritance and function. Fission and fusion of mitochondria have been found to be mediated by several large GTPases (e.g., Dnm1/DLP1/Drp1; Fzo1/Mfn1,2; Mgm1/OPA1, in yeast and mammals, respectively) [78,79] (articles by J. Nunnari and A. van der Bliek, this issue) (Table 1). Members of the dynamin family of large GTPases have been implicated in tubulation and fission events of cellular membranes, either as a molecular switch or as a pinchase-like mechanoenzyme [80–83]. Dynamin is a 100-kDa large GTPase that participates in membrane scission in multiple endocytic and secretory organelles [84]. Recent in vitro studies have indicated that conventional dynamin has the ability to tubulate spherical liposomes and, upon GTP hydrolysis, constrict, deform or sever membrane tubules into discrete vesicles [85–88]. The dynamin-like proteins Dnm1 (yeast), DRP-1 (*C. elegans*), and DLP1/Drp1 (mammals) are homologues involved in the mitochondrial fission process [58,89–92] (Table 1). They have been observed to concentrate at tips and constrictions of the outer mitochondrial membrane which leads to final membrane fission [89,93]. Like conventional dynamin, mammalian DLP1/Drp1 forms a homotetrameric complex in the cytosol [94], and is able to form rings and tubulate membranes in a nucleotide-dependent manner both in living cells and in vitro [95].

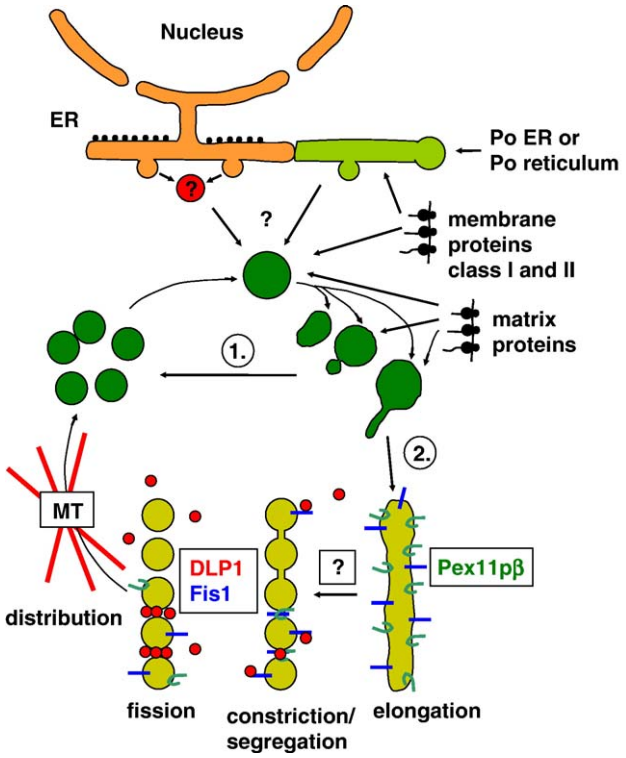

Fig. 2. Model of peroxisomal biogenesis and dynamics in mammalian cells. The potential role of the ER or a subcompartment of the ER in the formation of peroxisomes is included (see Section 2) The majority of the peroxisomal matrix and membrane proteins (Class I PMPs) are synthesized on free polyribosomes in the cytosol and imported post-translationally into pre-existing peroxisomes. Some membrane proteins (Class II PMPs, early peroxins) are presumably routed to peroxisomes via the ER or a pre-peroxisomal compartment. Peroxisomes can multiply by budding (1) and/or by elongation, segmentation and final fission, forming spherical peroxisomes (2). Pex11pβ is involved in the elongation/tubulation of peroxisomes (see Section 5.1), whereas DLP1/Drp1 and Fis1 mediate peroxisomal fission (see Section 4). Fis is supposed to recruit cytosolic DLP1/Drp1 to the peroxisomal membrane. Components involved in the constriction of peroxisomes are presently unknown. Proper intracellular distribution of the peroxisomes formed by fission requires microtubules and a functional dynein/dynactin motor [55]. In yeast and plants peroxisomes are distributed via the actin cytoskeleton [56,104,148].

Mitochondrial fission in yeast requires the interaction of the dynamin-related GTPase Dnm1p with Fis1p, a tail-anchored mitochondrial outer membrane protein, and the soluble molecular adaptors, Mdv1p, and Caf4p (reviewed in [79]) (Table 1). Mdv1p contains coiled-coil domains and seven C-terminal WD40 repeats predicted to form a β-propeller and to function in protein interaction. Caf4p domain structure is similar to Mdv1p. According to recent models, Fis1p appears to recruit Dnm1p to mitochondria through one of the two adaptors [96]. Dnm1p is observed to concentrate at division sites and to mediate a constriction process of the outer mitochondrial membrane which leads to final membrane fission. Homologues of Mdv1p and Caf4p have not yet been identified in higher eukaryotes, but homologues of Fis1p have been found, suggesting that the role of Fis1 in mitochondrial fission is conserved among lower and higher eukaryotes (Table 1). Evidence has been presented that hFis1, a human homologue of Fis1p, regulates mitochondrial fission in mammalian cells through an interaction with DLP1/Drp1. Overexpression of hFis1 causes mitochondrial fragmentation whereas inhibition or down-regulation induces mitochondrial elongation [97–100]. These observations indicate that hFis1 is a limiting factor in mitochondrial fission, and suggest that hFis1 serves as a membrane receptor that recruits DLP1/Drp1 (and/or other fission components) to mitochondria [97,100].

4.2. A role for DLP1/Drp1 in both peroxisomal and mitochondrial division

Recent studies have led to the surprising finding that the dynamin-like protein DLP1/Drp1 is involved in both mitochondrial as well as peroxisomal fission in mammals [73,101,102]. In addition to its mitochondrial localization, DLP1/Drp1 has been found to align in spots along elongated peroxisomes and to associate with the tips of some tubules [101]. Since the segmentation of elongated peroxisomes has been connected with peroxisomal fission [76,77], these morphological observations are consistent with a direct role of DLP1/Drp1 in peroxisomal division. Furthermore, DLP1/Drp1 was present in highly purified peroxisomal (and mitochondrial) fractions isolated from rat liver, and was co-immunopurified with peroxisome membranes [101,102]. The association of DLP1/Drp1 with peroxisomes was increased when peroxisome proliferation was induced, either by expression of Pex11pβ or by treatment of rats with the potent peroxisome proliferator bezafibrate. Expression of Pex11pβ has been shown to result in rapid elongation of peroxisomes, followed by segregation of peroxisomal proteins and formation of numerous small, punctiform peroxisomes [77] (see Section 5.1), thus representing a strong stimulus for peroxisome proliferation. Such a recruitment of DLP1/Drp1 to peroxisomes is expected under conditions of rapid growth and division of the peroxisomal compartment when DLP1/Drp1 is required for these processes. In line of this, inhibition of DLP1/Drp1 function by expression of dominant-negative DLP1/Drp1 mutants or down-regulation of DLP1/Drp1 by siRNA inhibited peroxisomal and mitochondrial fission and caused elongation of both organelles [101,102]. Peroxisomal tubules measuring 5 μm up to 15 μm in length were frequently observed (Fig. 1). 'Hypertubulation' of peroxisomes (up to 40 μm in length) and the formation of tubulo-reticular networks of peroxisomes was observed, when Pex11pβ was expressed in cells silenced for DLP1/Drp1 (or co-expressing dominant-negative DLP1/Drp1-K38A) [73,101]. This may suggest that fusion of elongated peroxisomes was promoted under these conditions. In summary, these findings provide strong evidence for a role of DLP1/Drp1 in both peroxisomal and mitochondrial division in mammalian cells (Fig. 2).

The requirement of dynamins for peroxisome division also extends to higher plants, as the dynamin-related protein DRP3A has been implicated in both peroxisomal and mitochondrial division in *Arabidopsis thaliana* [103]. In glucose-grown yeast, the division of peroxisomes is supposed to require the dynamin-related protein Vps1, which plays an additional role in vacuole biogenesis [104] (Table 1). In cells lacking Vps1, the number of

Table 1
Mitochondrial and peroxisomal morphology proteins in yeast and mammals

Mitochondria			Peroxisomes			Function
Yeast protein	Mammals (homolog)	Location	Yeast protein	Mammals	Location	
Dnm1	Drp1/DLP1	Cytosol		Drp1/DLP1	Cytosol	Fission
		OMM peripheral	Vps1		PoM peripheral	
Fis1	hFis1	OMM integrated		hFis1	PoM integrated	Fission
Mdv1		Cytosol				Fission
		OMM peripheral				
Caf4		Cytosol				Fission
		OMM peripheral				
	Endophilin B1	Cytosol				Fission
		OMM peripheral				
	MTP18	intramitochondrial				Fission
			Pex1	Pex1	AAA-ATPases	Membrane
			Pex6	Pex6		Fusion
Fzo1	Mfn1/2	OMM integrated				Fusion
Mgm1	OPA1	IMS peripheral/				Fusion
		IMM integrated?				
Ugo1		OMM integrated				Fusion
			Pex11	Pex11α, β (γ)	PoM integrated	Tubulation,
			Pex25			Regulation of
			Pex27			size and number
Mmm1		OMM/IMM-spanning				Tubulation
Mdm10, Mdm12		OMM integrated				Tubulation
Mmm2		OMM integrated				Tubulation
Mdm31, Mdm32		IMM integrated				Tubulation
Mdm33		IMM integrated				IMM fission?
			Pex28		PoM	Separation?
			Pex29			Regulation of
						size and number
			Pex30		PoM	Regulation of
			Pex31			size and number
			Pex32			
			Pex16		Intraperoxisomal	Curvature?

OMM, outer mitochondrial membrane; IMM, inner mitochondrial membrane; IMS, intermembrane space; PoM, peroxisomal membrane; Pex, peroxin. For details, see text.

peroxisomes is reduced, and peroxisomes appear as large tubular structures. Interestingly, peroxisomes in *vps1*Δ cells are still able to divide, but peroxisome division under these growth conditions does not require Mgm1 or Dnm1, the two other dynamin-like proteins of *S. cerevisiae* [104].

4.3. Peroxisomal and mitochondrial membrane constriction

Interestingly, the elongated peroxisomes observed after silencing of DLP1/Drp1 (see Section 4.2) had a segmented morphology, resembling 'beads on a string' (Fig. 1). Ultrastructural and quantitative studies confirmed that the elongated peroxisomes retained the ability to constrict their membranes after down-regulation of DLP1/Drp1, but were not able to divide into spherical organelles [73]. Thus, DLP1/Drp1 is not required for peroxisome constriction, but only for final scission. It is assumed that initial peroxisome constriction and final scission are distinct processes, which use distinct sets of molecular components (Fig. 2). Since a peroxisomal tubule has an average diameter of approximately 100±20 nm, constriction may cause a thinning of the membrane tubule to favor the association of DLP1/Drp1 (and additional factors) around the tube. It is likely that constriction of the peroxisomal membrane takes place before DLP1/Drp1 recruitment, which is then followed by subsequent peroxisomal fission. The molecular components mediating peroxisomal constriction are greatly unknown. It is likely that constriction is influenced by the local composition of lipids, which determines lateral strength and curvature of the membrane. In this context, lipid-modifying enzymes may be involved, as demonstrated for endocytic vesicle formation [105,106]. One example of a protein that could remodel lipids in the peroxisomal membrane by a regulated interaction with acyl-CoA oxidase (AOX) and thus, control membrane constriction from within the peroxisome, is Pex16p from the yeast *Y. lipolytica* [107] (Table 1).

It is still a matter of debate whether DLP1/Drp1 is required for both the initial constriction and the final scission step in mitochondria, and whether distinct sets of proteins/components are involved [108–110]. Recently, Mdm33, a component which might be involved in mitochondrial constriction in *S. cerevisiae*, has been identified [111]. Furthermore, mitochondrial structures which resemble the peroxisomal 'beads on a string' have been observed in *C. elegans* DRP-1 mutants [90]. In red algae, Dnm1 seems to accumulate on the mitochondria after FtsZ-mediated

constriction of the inner membrane has occurred, and seems to cleave the thin tubule connecting the dividing organelles [112]. Moreover, in yeast, mitochondrial constriction can occur independently of fission, indicating that Dnm1 is not required for the constriction process [108]. It has to be demonstrated whether this is also the case for DLP1/Drp1 on mammalian mitochondria.

4.4. hFis1—the receptor for DLP1/Drp1 on mitochondria and peroxisomes

The mitochondrial outer membrane protein Fis1p/hFis1 is a small 17 kDa protein with a single transmembrane domain at the C-terminal end [113]. A large part of Fis1p/hFis1 is facing the cytosol where it is supposed to interact with cytosolic proteins such as Dnm1/DLP1/Drp1, Mdv1p and Caf4p (reviewed in [79,97,100]). Structural analyses of hFis1 revealed that the N-terminal cytosolic domain contains an N-terminal arm and an antiparallel array of six α-helices, which form a tetratricopeptide repeat (TPR)-like fold. It is suggested that its hydrophobic concave surface serves as a binding pocket to mediate protein–protein interactions [114,115]. The six α-helices of yeast Fis1 form a TPR-like fold similar to that of hFis [116]. However, the N-terminal arm of hFis1 appears to be flexible, whereas the extended, N-terminal arm of yeast Fis1 is partially fixed to the concave surface of the TPR motif. It is supposed that functional divergence of the cytoplasmic domain has occurred during evolution [99]. A recent study indicates that the TPR region of hFis1 participates in the interaction with DLP1/Drp1 (or a DLP1/Drp1 containing complex), and that the N-terminal α1-helix of hFis1 is required for mitochondrial fission presumably by regulating DLP1/Drp1–hFis1 interaction [100].

We have made the exciting observation that in addition to DLP1/Drp1, hFis1 is also involved in the proper division of peroxisomes [117]. Besides its mitochondrial localization, endogenous and exogenously expressed hFis1 has been found to be targeted to peroxisomes. Unlike DLP1/Drp1, which is concentrated in spots, hFis1 distributes evenly along the membranes of peroxisomes and mitochondria. Fis1 was also detected in highly purified peroxisomal (and mitochondrial) fractions isolated from rat liver, and the association of rat Fis1 with peroxisomes was increased when peroxisome proliferation was induced by bezafibrate [117]. Inhibition of hFis1 function by siRNA caused a fission defect similar to DLP1/Drp1-defective cells leading to the formation of elongated peroxisomes and mitochondria. Most notably, the ectopic expression of hFis1 promoted peroxisomal and mitochondrial division resulting in the accumulation of fragmented mitochondria and very small, punctiform peroxisomes, which resembled those induced by Pex11pβ expression. Furthermore, the induction of peroxisomal and mitochondrial division by hFis1 required a functional DLP1/Drp1.

Through differential tagging and deletion experiments, we could demonstrate that the transmembrane domaine and the short C-terminal tail of hFis1 is both necessary and sufficient for its targeting to peroxisomes and mitochondria, whereas the N-terminal region is required for organelle fission and dispensable for localization [117]. Whereas soluble matrix proteins which are targeted to both peroxisomes and mitochondria are known [118,119], hFis1 is one of the few transmembrane proteins described so far, which is targeted to both organelles in mammalian cells [120]. As details about the insertion of membrane proteins into peroxisomes are just beginning to emerge (see Section 2), we can currently not answer to the interesting question how this dual targeting is achieved. We speculate that it is mediated by the different import machineries, and not primarily by the information in the hFis1 sequence.

Based on the above observations, it is likely that hFis1 fulfils similar functions during peroxisomal and mitochondrial division. Further expression of DLP1/Drp1 which is abundant in the cytosol, does not induce peroxisomal (and mitochondrial) fission [73,121] indicating that a molecular adaptor/regulator is required. As suggested recently [100], hFis1 may be a main regulator of mitochondrial (and peroxisomal) division by orchestrating the recruitment and assembly of DLP1/Drp1 during the fission process (Fig. 2). It is possible (and likely) that hFis1 interacts with other, yet unknown proteins to regulate the DLP1/Drp1–hFis1 interaction. While no Mdv1p- or Caf4-like proteins have been found in mammalian cells so far, the identification of other Fis1-interacting proteins (Fip) on mitochondria has been reported. The 47-kDa protein Fip1 appears to be a novel component of the mitochondrial fission machinery [122]. It is highly conserved among higher eukaryotes as well as some fungi, but is lacking from *S. cerevisiae*. Fip1 knockdown results in an elongation of mitochondria (but not peroxisomes) suggesting that its absence inhibits the fission process. As hFis1 and DLP1/Drp1 are shared components of mitochondrial and peroxisomal division, it is reasonable to speculate that Fis1 interacting proteins specific for mitochondria (mFip) and peroxisomes (pFip) may exist, which regulate the assembly of the fission machineries.

5. Unique components of peroxisomal and mitochondrial dynamics and division

5.1. Pex11p—a membrane tubulator?

The growing family of Pex11 proteins are involved in the regulation of peroxisomal growth in size and number, and have been proposed to function in peroxisome division in lower and higher eukaryotes (reviewed in [123,124]). Pex11p-deficient cells contain a small number of enlarged peroxisomes, whereas overexpression results in a high degree of peroxisome proliferation [77,125–129]. Mammalian cells express at least three distinct Pex11 genes (Pex11pα, β, γ), which are supposed to control peroxisome proliferation under induced and basal conditions, respectively [77,128–131]. Pex11pα, β, γ are transmembrane proteins with their N- and C-termini exposed to the cytosol, which are likely to form homo-oligomers or homodimers [102,126]. When overexpressed, Pex11pβ induces peroxisome proliferation through a multistep process involving peroxisome elongation and segregation of Pex11pβ from other peroxisomal proteins, followed by peroxisome division [77]. *S. cerevisiae* has a single Pex11 gene [132], but recent findings

indicate that Pex25p and the novel peroxin Pex27p are Pex11p-related proteins, which are involved in the regulation of peroxisome size and number in yeast [133–135] (Table 1).

Recent studies indicate that Pex11pβ is still able to induce growth and enlargement of the peroxisomal compartment in the absence of DLP1, but is itself not capable of dividing or constricting peroxisomal membranes. We therefore propose a major function for Pex11pβ in the enlargement and modification of the peroxisomal membrane prior to division rather than in the fission process itself [73,101] (Fig. 2). Similarities of the yeast Pex11p with the ligand-binding domain of nuclear hormone receptors might point to a role in phospholipid-binding [136]. However, the biochemical properties of Pex11p are still a matter of debate [124]. Although a direct interaction between DLP1 and Pex11p has not been detected [102], the membrane modifying activity of Pex11p might support the recruitment of the fission machinery to peroxisomes through an indirect mechanism. Furthermore, Fis1 and Pex11p were not found to be part of a common complex, but co-expression of both proteins disturbed the normal uniform intracellular distribution of peroxisomes [117].

These observations further suggest that peroxisomal elongation, constriction and fission require distinct sets of proteins/components, and that tubule formation of peroxisomes is an important prerequisite of peroxisome division [73,76] (Fig. 2). Interestingly, several mitochondrial membrane proteins (e.g., Mmm1p, Mdm10p, Mdm12p) have been identified in fungi but not in higher eukaryotes, which are required for the formation of mitochondrial tubules (Table 1). When this tubulation pathway is disrupted, mitochondria form large spheres (reviewed in [79]) (see article by N. Pfanner, this issue).

5.2. Endophilin B1 and MTP18

Endophilin B1, a putative fatty acyl transferase, has recently been reported to be required for the maintenance of mitochondrial morphology in mammalian cells, especially for the remodelling of the outer mitochondrial membrane [137] (Table 1). It was found to partially colocalize and cofractionate with mitochondria. Endophilin B1 down-regulation or expression of a truncated endophilin B1 lacking the putative lipid-modifying domain caused changes in mitochondrial shape, the dissociation of the outer and inner mitochondrial membrane and the formation of outer mitochondrial membrane-bound tubules and vesicles. Members of the endophilin protein family (for example, amphiphysin, endophilin 1, BARS-50) are supposed to participate in the regulation of membrane curvature, a process required for membrane scission [105,106]. However, the functional role of endophilin and related components has recently been questioned [138]. The morphology and distribution of peroxisomes appeared not to be influenced by knockdown of endophilin B1 [137] or by expression of a truncated variant of endophilin B1 (M. Schrader, unpublished observation).

MTP18, a nuclear-encoded mitochondrial membrane protein, is also suggested to be a novel component for mitochondrial fission in mammalian cells [139,140] (Table 1). Interestingly, MTP18 is supposed to be an intramitochondrial protein exposed to the intermembrane space. Overexpression of MTP18 caused DLP1/Drp1-dependent mitochondrial fragmentation, whereas a loss-of function resulted in highly fused mitochondria. Moreover, hFis1-induced mitochondrial fission was blocked after silencing of MTP18. MTP18 appears to be specific for mitochondrial fission, as it does not localize to peroxisomes. Furthermore, peroxisomal morphology is not greatly altered after overexpression of full-length MTP18, or truncated variants (M. Schrader, unpublished observations).

6. Peroxisomal and mitochondrial cooperation and coevolution

There is growing evidence that peroxisomes and mitochondria are metabolically linked organelles, which are cooperating and cross-talking. Mitochondria and peroxisomes have a key role in both the production and scavenging of reactive oxygen species (ROS), which have important functions in cellular signalling [26–28]. In animals (including humans), both peroxisomes and mitochondria harbour a β-oxidation system and interact functionally in the oxidation of fatty acids, and in thermogenesis (reviewed in [34,141,142]). It has to be noted that in yeast and in plant cells, peroxisomes are the only site of β-oxidation [143] making them essential for the utilization of fat in these organisms. A metabolic link between peroxisomes and mitochondria is also found in certain yeasts grown on fatty acids or alkanes, where the enzymes of the glyoxylate cycle are shared, and in plant leaves where the organelles tightly cooperate in the diversion of glycolate, produced by photosynthesis, into glycine and serine production, resulting in photorespiration [22,23]. Such a metabolic communication renders peroxisomes and mitochondria dependent upon each other for their function. It further requires a coordinated biogenesis and turnover.

An endosymbiotic origin, which is generally accepted for mitochondria, has also been proposed for peroxisomes. However, recent findings on the de novo formation of peroxisomes suggest that the original peroxisome was possibly derived from a cellular membrane system such as the endoplasmic reticulum as an invention of the eukaryotic cell (reviewed in [144]). It is possible that the peroxisomes were already present when the promitochondria colonised the early eukaryotic cell. Enzyme mislocations between peroxisomes and mitochondria are supposed to have occurred during evolution giving rise to the analogous metabolic pathways in both organelles. As mitochondria appear to have lost division components of their bacterial origin [145] (see also article by T. Kuoriwa, this issue), they may even have coopted the main components of their outer membrane fission machinery from peroxisomes (and other membrane compartments of the pro-eukaryotic cell).

7. Perspectives

The discovery that DLP1/Drp1 and hFis1 are required for peroxisomal (and mitochondrial) fission has opened the field for

the molecular characterization of the peroxisomal division machinery. Although both mitochondria and peroxisomes utilize some organelle-specific components for membrane division and maintenance of morphology, it is reasonable to speculate that they might have other components of the fission machinery in common. It is an interesting question, how the dual targeting of these components is mediated, and how the assembly of the division machinery on both peroxisomes and mitochondria is regulated. In contrast to mitochondria, peroxisomes have to divide a single limiting membrane only. Therefore, they might represent a simpler model (however, not less complex) for the understanding of organelle fission. Further studies of DLP1/Drp1-mediated organelle fission should also be of considerable value for the understanding of peroxisomal biogenesis. It may be possible that dynamin-related proteins are also involved in the biogenesis of peroxisomes as they emanate from the ER or a pre-peroxisomal compartment.

Studying peroxisomal (and mitochondrial) morphology and dynamics is certainly one of the exciting fields because of its relation to peroxisomal (mitochondrial) functionality. There is growing evidence that in addition to the regulation of organelle morphology, mitochondrial dynamics play additional roles in mitochondrial function [59,109] such as electron transport and regulation of apoptosis. It is further assumed that the close link between morphology and function has an impact on cell and tissue physiology, for example on embryonic development, cell death, neurodegeneration and aging [59,146]. Peroxisomes orchestrate important functions during development [147], and peroxisome proliferation as well as dysfunctions are linked to tumor formation, neurodegeneration and aging. It is an exciting question, if and how peroxisomal morphology and dynamics influence peroxisomal functions as well as developmental and physiological processes.

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